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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
AEDER, SEAN E	

ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
08/14/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/646,784	MAHESWARAN ET AL.	
	Examiner	Art Unit	
	SEAN E. AEDER	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,14-28 and 31-35* is/are pending in the application.

4a) Of the above claim(s) *35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11, 14-28, and 31-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/9/08 has been entered.

Claims 1-11, 14-28, and 31-35 are pending.

Claim 35 has been withdrawn.

Claims 1, 6-9, 18, 26 have been amended by Applicant.

Claims 1-11, 14-28, and 31-34 are currently under consideration.

Objections Withdrawn

The objections to claims 9 and 26 are withdrawn.

Rejections Withdrawn

The rejection under 35 U.S.C. 112, first paragraph, is withdrawn.

Response to Arguments

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-11, 14-16, 18-28, and 31-33 remain rejected under 35 U.S.C. 102(b) as being anticipated by Donahoe et al (US Patent 5,661,126; 8/26/97) for the reasons stated in the Office Action of 10/3/06, the Office Action of 7/11/07, and for the reasons set-forth below.

Donahoe et al teaches a method comprising administering MIS and interferon to a patient having has a tumor selected from the group consisting of vulvar epidermoid carcinoma, cervical carcinoma, endometrial adenocarcinoma, ovarian adenocarcinoma, ocular melanoma, prostate tumor, breast tumor, cutaneous tumor, or germ cell tumor (see column 1 lines 24-27, column 15 lines 43-50, and column 21 lines 25-38, in particular). The claimed method is the same as the method taught by Donahoe et al, therefore the method taught by Donahoe et al would result in decreased side-effects, thereby increasing anti-tumor effect of interferon. Donahoe et al further teaches said method wherein said patient has primary tumor growth or metastatic tumor growth (see column 15 lines 47-50, in particular). Donahoe et al further teaches a method wherein MIS has a molecular weight of 140 kDa or 70 kDa (see column 1 lines 44-49, in particular). Donahoe et al further teaches a method wherein said MIS is proteolytically cleaved by reacting with a proteolytic compound to form protein fragments having a

molecular weight of about 57 kDa and 12.5 kDa (see column 1 lines 49-54, in particular). Donahoe et al further teaches a method wherein MIS is rhMIS (see Example 3, in particular). Donahoe et al further teaches a method wherein said MIS is C-terminal fragment of MIS substantially free of N-terminal fragment (see column 2 lines 39-54, in particular). Donahoe et al further teaches a method wherein said C-terminal fragment of MIS has a molecular weight of about 25 kDa or about 12.5 kDa 9 (see column 2 lines 39-42, in particular). Donahoe et al further teaches a method wherein the C-terminal fragment of MIS is derived from rhMIS (see Example 3, in particular). Donahoe et al further teaches a method wherein interferon is selected from the group consisting of interferon-α, interferon-β, interferon-ω, interferon-τ, and interferon-γ (see column 21 lines 26-40 and column 26 lines 34-36, in particular). Donahoe et al further teaches a method wherein said interferon is interferon-γ (see column 26 lines 34-36, in particular). Donahoe et al further teaches interferon-γ decreases metastatic competence of tumor cells (lines 33-36 of column 22, in particular). Donahoe et al further teaches therapeutic effects of MIS can be achieved or enhanced by the additional administration of an agonist of MIS or an antagonist of EGF (see paragraph spanning columns 26-27). Donahoe et al further teaches interferon-γ is an agonist of MIS and that interferon is an EGF antagonist (see lines 35-36 and 45-46 of column 26, in particular). Donahoe et al further teaches "MIS can be co-administered with interferon (or other agonists) in order to increase the effectiveness of the therapy" (lines 18-20 of column 27, in particular). Donahoe et al further teaches a method wherein interferon would be effective between about 0.001 and 10.0 mg/kg body weight of a

patient, which is an amount of about 10 international units per administration to an amount of about 100,000 international units per administration (see column 21 lines 16-20, in particular).

In the reply of 6/9/08, Applicant argues that Donahoe et al does not teach use of interferon-γ as a chemotherapeutic agent which can be used as an agonist to increase the anti-tumor effect of MIS. Applicant further argues that interferon-γ was only known as a cytokine or MHC Class I modulating molecule and not as a chemotherapeutic agent at the time of filing the current application. Applicant further argues that Donahoe et al does not teach use of a decreased quantity of interferon-γ for reduced side effects when interferon-γ as a therapeutic agent as claimed. Applicant further argues that the teachings of Donahoe et al would not teach use of interferon-γ in combination with MIS for an additive effect on the treatment of the tumor. Applicant further states that Donahoe et al teaches an inhibitor of interferon-γ could be used as an agonist to MIS. Applicant then cites lines 34-36 on column 26 of Donahoe and implies that Donahoe et al teaches administration of MIS with inhibitory antibodies to interferon-γ.

The amendments to the claims and the arguments found in the Reply of 6/9/08 have been carefully considered, but are not deemed persuasive. In regard to the arguments that Donahoe et al does not teach use of interferon-γ as a chemotherapeutic agent which can be used as an agonist to increase the anti-tumor effect of MIS and that Donahoe et al would not teach use of interferon-γ in combination with MIS for an additive effect on the treatment of the tumor, Donahoe et al teaches therapeutic effects of MIS can be achieved or enhanced by the additional administration of an agonist of

MIS or an antagonist of EGF (see paragraph spanning columns 26-27). Donahoe et al further teaches interferon-γ is an agonist of MIS and that interferon is an EGF antagonist (see lines 35-36 and 45-46 of column 26, in particular). Donahoe et al further teaches "MIS can be co-administered with interferon (or other agonists) in order to increase the effectiveness of the therapy" (lines 18-20 of column 27, in particular).

In regards to the argument that interferon-γ was only known as a cytokine or MHC Class I modulating molecule and not as a chemotherapeutic agent at the time of filing the current application, interferon-γ was known at the time of filing to decrease the metastatic competence of tumor cells (lines 33-36 of column 22, in particular). Further, interferon-γ was known at the time of filing to increase the effectiveness of MIS therapy (see lines 35-36 and 45-46 of column 26 and lines 18-20 of column 27, in particular).

In regards to the argument that Donahoe et al does not teach use of a decreased quantity of interferon-γ for reduced side effects when interferon-γ as a therapeutic agent as claimed, as evidenced by Kurzrock et al (Cancer Research, June 1985, 45:2866-2872), dose-limiting toxicities of high fever and generalized weakness (i.e. a "side effects") for patients that are administered interferon-γ occur above 2.5 mg/sq m (which, using a Km of 37, is about 92.5 mg/kg – a dose much greater than taught by Donahoe et al) (see right column of page 2871, in particular). Therefore, the method of Donahoe et al uses an effective amount of interferon-γ that results in decreased side effects, such as high fever and general weakness, associated with interferon-γ.

In regards to the argument that Donahoe et al teaches an inhibitor of interferon-γ could be used as an agonist to MIS, no such teaching is found in Donahoe et al.

Rather, Donahoe et al teaches interferon-γ is an agonist of MIS (see lines 34-36, in particular).

In regards to the citation of lines 34-36 on column 26 of Donahoe and argument that Donahoe et al teaches administration of MIS with inhibitory antibodies to interferon-γ, Donahoe et al does not teach administration of MIS with any type of antibodies to interferon-γ. Lines 34-36 of column 26 recite methods where interferon-γ is administered as an agonist of MIS. The only antibodies taught by Donahoe et al that would be administered with MIS are antibodies to EGF (see lines 34-36 of column 26). Donahoe et al further clarifies that interferons are agonists of MIS at line 19 of column 27.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-11, 14-28, and 31-34 remain rejected under 35 U.S.C. 103(a), as being unpatentable over Donahoe et al (US Patent 5,661,126; 8/26/97) in view of Cohen (Int. J. Radiation Oncology Biol. Phys., 2/87, 13(2): 251-258), for the reasons stated in the Office Action of 10/3/06, the Office Action of 7/11/07, and for the reasons set-forth below.

Claims 1-16 and 18-33 are described above. Claim 17 is drawn to the method of claim 1, wherein said interferon is administered in an amount less than 1 x 10^6 International Units per administration. Claim 34 is drawn to the method of claim 18, wherein said interferon is administered in an amount less than 1 x 10^6 International Units per administration.

The teachings of Donahoe et al are described above.

Cohen teaches that in successful cancer therapy, the tumor must be eradicated without significant damage to adjacent tissues or organs (page 251). Cohen teaches a method of optimizing dosages of compounds used to treat tumors (page 251, in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer MIS and interferon to a cancer patient as taught by Donahoe et al and optimize the amounts of MIS and interferon in said administration as taught by Cohen. Further, one would have been motivated to administer interferon at doses below 1 x 10^6 International Units per administration since Donohue et al indicates that a low dose of interferon, in combination with MIS administration, would predictably treat tumors. Further, one of skill in the art would have a reasonable expectation of success in performing the claimed methods since administration of MIS and interferon is well known and conventional in the art.

In the Reply of 6/9/08, Applicant repeats arguments addressed above. Further, Applicant cites Pieretti-Vanmarke et al (PNAS, 2006, 103:17426-31) and argues that MIS cannot be used in combination with all chemotherapeutic agents to decrease the

dose of such therapeutic agents. Applicant further argues that Donahoe et al does not distinguish which chemotherapeutic agents can be combined with MIS to reduce their side effects and does not teach the use of MIS in combination with carefully selected chemotherapeutic agents to reduce their side effects. Applicant further argues that without the knowledge of which selected chemotherapeutic agents could be used in combination to reduce the dose, modifying the teachings of Donahoe et al and Cohen et al would not reasonably be expected to succeed at the time of the invention.

The amendments to the claims and the arguments found in the Reply of 6/9/08 have been carefully considered, but are not deemed persuasive. In regards to argument that MIS cannot be used in combination with all chemotherapeutic agents to decrease the dose of such therapeutic agents, the examiner agrees that MIS cannot be used in combination with all chemotherapeutic agents to decrease the dose of such therapeutic agents. However, as stated above, Donahoe et al teaches the claimed method of using MIS in combination with interferon-γ.

In regards to (1) the argument that Donahoe et al does not distinguish which chemotherapeutic agents can be combined with MIS to reduce their side effects and does not teach the use of MIS in combination with carefully selected chemotherapeutic agents to reduce their side effects and (2) without the knowledge of which selected chemotherapeutic agents could be used in combination to reduce the dose, modifying the teachings of Donahoe et al and Cohen et al would not reasonably be expected to succeed at the time of the invention, Donahoe et al teaches the claimed method using MIS in combination with interferon-γ and one of skill in the art would have a reasonable

expectation of success in administering MIS and interferon to a cancer patient as taught by Donahoe et al and optimizing the amounts of MIS and interferon in said administration as taught by Cohen since administration of MIS and interferon is well known and conventional in the art.

Summary

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SEAN E. AEDER whose telephone number is (571)272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sean E Aeder/
Examiner, Art Unit 1642